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Management of gout in advanced renal disease

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Abstract

Gout is the most common inflammatory arthritis, and its prevalence is increasing in part due to the rise in chronic kidney disease (CKD). Guidelines for managing gout from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) provide limited guidance for patients with advanced renal disease, partly due to the exclusion of this group of from clinical trials. This, along with concerns about adverse drug reactions contributes to the undertreatment of gout in advanced CKD. Gout management involves different phases: treatment of acute gout flares, implementing prophylaxis to prevent attacks and urate-lowering therapy (ULT). In this review, we examine the management of gout, with particular attention to recommended adjustments for patients with advanced CKD, those undergoing dialysis, or individuals who have received renal transplants. We review the medications used in the management of gout and suggest adjustments for their selection and dose in patients with advanced CKD. The article discusses colchicine, glucocorticoids, and IL1-β inhibitors for acute gout treatment and provides recommendations for flare prophylaxis. We review the use of xanthine oxidase inhibitors (allopurinol, febuxostat) and pegloticase as urate-lowering therapies for patients with advanced CKD, on dialysis, or with renal transplants. The possible side effects of gout treatments in patients with CKD and the suggested monitoring protocols are discussed. The potential impact of allopurinol, colchicine, and IL1-β inhibitors on cardiovascular disease outcomes are reviewed. Finally, new targets and drugs being explored for treating gout in patients with advanced CKD are discussed.

Keywords

Gout, chronic kidney disease, hyperuricemia, treatment

Introduction

Gout, the most common inflammatory arthritis, is caused by hyperuricemia and crystal deposition in tissues. The prevalence ranges from 0.1% in Nigeria to > 10% for people in Taiwan, China and Māori peoples of New Zealand [1–3]. This is in part due to global variation in the urate transporter genes *SLC2A9, ABCG2* and *S:C22A12* that regulate renal excretion of uric acid [4]. Diets high in purines contribute to gout as is demonstrated by the greater prevalence of gout among Filipinos emigrating to the United States where a higher purine diet and decreased activity are proposed contributing factors for the difference compared to residents in the Philippines where a more traditional diet is consumed [5]. The prevalence of gout is increasing due to global changes in diet as well as the rise in obesity, diabetes mellitus (DM) hypertension and metabolic syndrome. The rise in chronic kidney disease (CKD) is another major factor [6, 7]. CKD is associated with hyperuricemia and responsible for 39% of gout cases [8]. However, establishing causation is challenging: hyperinsulinemia from obesity and metabolic syndrome reduce urate excretion and is associated with CKD [9]. Hypertension may precede CKD and, through renal vasoconstriction, lead to uric acid retention [10]. Conversely, elevated serum uric acid (sUA) may promote the progression of CKD by inducing endothelial dysfunction, activation of the renin-angiotensin system (RAS) and resultant systemic and glomerular hypertension [11]. The incidence of gout in patients on dialysis is less clear with estimates that vary widely from < 3% to 15.4% [12, 13]. Kidney transplant recipients are known to have an increased risk of gout. New onset gout after transplant has been reported in 3.5–24% of recipients [14–17]. The prevalence of gout in the surviving kidney transplant population in 2017 was estimated to be 13.1% [18].

Clinically, there are several phases of gout, acute gout is a severe inflammatory condition, typically monoarticular, however, it can be oligo- or polyarticular. Acute gout results from pro-inflammatory responses to monosodium urate (MSU) crystals, mediated by the Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes in macrophages and monocytes, triggered by factors such as animal-derived purines, alcohol, diuretics, and stress, to name a few [19, 20]. It typically presents as an acute onset arthritis with swelling, redness, warmth, and limitation of movement peaking within 12–24 hours. Periarticular involvement can manifest as bursitis, dactylitis, enthesitis, tenosynovitis, or cellulitis. While some patients may have mild and rapidly self-limited inflammatory episodes, most require pharmacologic treatment for symptom resolution. The attacks are interspersed by asymptomatic or intercritical periods. If only symptoms are addressed, attacks become more frequent and chronic tophaceous gout develops. The collections of urate crystals produce chronic inflammation and resultant destruction of the adjacent bone and soft tissue [21]. The tophi may occur adjacent to the joint, in a bursa or other periarticular structures, they are classically non-tender but signs of chronic inflammation can be present and superimposed acute attacks are common [22].

The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) provide little direction to medical practitioners for treating patients with gout and CKD due in part to the exclusion of these patients from clinical trials. This along with concerns about adverse drug reactions results in the undertreatment of these patients leading to more frequent attacks and the development of chronic gouty arthritis and tophi [23–26].

The management of gout should address all phases: treatment of acute gout flares, prophylaxis to prevent attacks and urate-lowering therapy (ULT). Herein, we discuss the evidence for the management of gout and provide suggestions for adjusting therapy in patients with advanced CKD.

Methods

We defined advanced CKD as patients with an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2 or Stage IV and V renal disease for the purposes of our manuscript [27]. PubMed and the Cochrane database were the primary data sources. They were searched from 1970 through October 2024 for articles that included the following terms for: (1) Gout (Gout or hyperuricemia or gouty arthritis or sUA) and (2) CKD [CKD, end stage kidney disease (ESKD), end stage renal disease (ESRD), hemodialysis,

peritoneal dialysis, advanced kidney disease, stage IV renal disease, stage V renal disease stage IV kidney disease, stage V kidney disease, chronic kidney failure, chronic renal failure]. The search was further refined by selecting articles that included the following medications: allopurinol, febuxostat, pegloticase, colchicine, corticosteroids, glucocorticoids, prednisone, prednisolone, methylprednisolone, anakinra, rilonacept, and canakinumab. The titles and abstracts were reviewed and articles relevant selected for further examination. The references for the selected articles were reviewed to find additional clinical trials, case reports, reviews, or guidelines relevant to the question.

Management of acute gout in patients with advanced CKD

The treatment options in patients experiencing an acute gout attack include colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids (oral, intra-articular, or intramuscular). In addition, IL-1 inhibitors and adrenocorticotropic hormone (ACTH) have also been utilized in managing acute gout [23]. Local measures including ice packs and rest may provide additional benefit [28].

In patients with advanced CKD, stage 4 or greater (GFR ≤ 30 mL/min/1.73 m^2), there appear to be multiple challenges in treating with usual pharmacologic options. Decreased glomerular filtration rate alters the pharmacokinetic properties of the drugs, especially clearance from the body leading to an increased risk for adverse events. The pharmacologic treatment of acute gout in advanced CKD requires appropriate selection of agents, suitable dosing adjustments and therapeutic monitoring [29, 30]. Below, we review some of the drugs used in the management of acute gout.

Nonsteroidal anti-inflammatory drugs

While the use of NSAIDs in patients with CKD should be avoided as much as possible, their use with caution is acceptable in smaller doses and for shorter treatment durations, especially in patients with GFR 30–60 mL/min/1.73 m^2 [29, 31]. Patients with DM, Hypertension, heart failure or who use diuretics or angiotensin-converting enzyme (ACE) inhibitors are at greater risk for acute kidney injury (AKI) and NSAIDs should be avoided or used with extreme caution even in mild CKD with monitoring of renal function. In healthy individuals, prostaglandins play a minimal role in maintaining renal hemodynamics. Consequently, the administration of NSAIDs, potent inhibitors of prostaglandin synthesis, is unlikely to have a significant impact on renal function. Diuretics are used to good effect in patients with congestive heart failure or hypertension but lower plasma volume. The addition of ACE inhibitors and NSAIDs to diuretics, the triple whammy, lowers trans glomerular hydrostatic pressure by blocking renal autoregulation leading to AKI [32, 33]. However, in patients with GFR ≤ 30 mL/min/1.73 m^2, NSAIDs are contraindicated due to adverse renal effects such as acute renal failure, nephrotic syndrome, interstitial nephritis, papillary necrosis, rhabdomyolysis and electrolyte disturbances from reduced potassium and sodium excretion [34]. NSAIDs should be used with caution if at all in kidney transplant recipients treated with calcineurin inhibitors, even those with near normal GFR due to the risk of AKI [35, 36]. In patients on dialysis, especially those who are anuric, renal side effects may be of less concern, but it is still prudent to limit long-term use due to the risk of adverse cardiovascular and gastrointestinal effects.

Colchicine

Colchicine is a lipophilic alkaloid drug that exhibits anti-inflammatory and anti-fibrotic properties through disruption of the microtubule system and inhibition of neutrophil adhesion and recruitment [37]. Colchicine is efficacious within the first 36 hours from the onset of symptoms of acute gout, at a dose of 1.2 mg followed by 0.6 mg one hour later (Table 1). After initial dosing, colchicine can be continued once or twice daily until the resolution of symptoms in patients with normal renal function [19]. This initial dosing schedule can be safely administered in patients with advanced CKD if not repeated more than once within a 2-week interval. For patients with advanced CKD, a reduced dose of 0.3 to 0.6 mg every other day, or 0.6 mg three times a week, can be used in individuals with lingering symptoms of the acute attack. Since colchicine undergoes partial renal clearance, there is potential for increased toxicity in patients with advanced CKD including anorexia, nausea, vomiting, diarrhea, rhabdomyolysis, neuropathy, myopathy, and bone marrow

suppression. Colchicine is not cleared by dialysis. It can be used for treatment of acute gout flares in dialysis patients with a single dose of 0.6 mg, not to be repeated for 14 days (Table 1). Colchicine has also been noted to interact with various drugs such as statins, non-dihydropyridine calcium channel blockers, calcineurin inhibitors (such as cyclosporine) and macrolides that typically increase the half-life of colchicine leading to increased toxicity [30, 38].

Table 1. Overview of drugs used to treat acute gout

Drug	Dosing regimen for acute gout			
	Normal renal function	Advanced CKD (eGFR ≤ 30 mL/min/1.73 m^2)	Dialysis	Renal transplant
Colchicine	1.2 mg at onset followed by 0.6 mg one hour later. Then 0.6 mg twice daily	1.2 mg at onset followed by 0.6 mg one hour later (do not repeat for 14 days)	0.6 mg once at the onset (do not repeat for 14 days)	Avoid secondary to interactions with several drugs used in transplant recipients
Prednisone	0.5 mg/kg/day followed by a taper over a few days	0.5 mg/kg/day followed by a taper over a few days	0.5 mg/kg/day followed by a taper over a few days	0.5 mg/kg/day followed by a taper over a few days
Anakinra	100 mg SC daily for 3–5 days	100 mg SC daily for 3–5 days or 100 mg every other day for 3–5 days	100 mg SC daily for 3–5 days or 100 mg every other day for 3–5 days	100 mg SC daily for 3–5 days
Canakinumab	150 mg SC once	150 mg SC once	150 mg SC once	150 mg SC once

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SC: subcutaneous

Glucocorticoids

Glucocorticoids exert their anti-inflammatory effects by reducing the expression of pro-inflammatory genes by activation of glucocorticoid receptors and the concomitant inhibition of pro-inflammatory transcription factors such as nuclear factor kappa-B (NF-κβ) and activating protein-1 (AP-1) [39]. Glucocorticoids (administered either orally or via the intramuscular, intravenous, or intra-articular route) are the preferred modality of treatment for the management of acute gouty arthritis in patients with advanced CKD. There is no consensus about the most effective dosing regimen for glucocorticoids, although it may be reasonable to start with 0.5 mg/kg of body weight daily for the first few days followed by dose tapering (Table 1) [19]. A short course of glucocorticoids has been noted to have a similar efficacy as NSAIDs in patients with acute gout and CKD, making it a safe modality of treatment in these patients [40]. There have been no randomized trials comparing the efficacy of glucocorticoids and colchicine for the treatment of acute gouty arthritis in patients with CKD. Systemic glucocorticoids should be avoided in patients with brittle diabetes where even short courses may precipitate diabetic ketoacidosis. Caution should also be employed in patients with uncontrolled hypertension, congestive heart failure or untreated infections. In patients with the above-mentioned comorbidities, especially those with a monoarticular gout flare, intra-articular administration of glucocorticoids is comparatively safer and preferred given a lower incidence of adverse effects.

Interleukin-1 inhibitors

Interleukin-1 inhibitors target the NLRP3 inflammasomes and prevent the action of interleukin-1 beta on cells, thereby exerting an anti-inflammatory action in the affected joint [39]. Interleukin-1 inhibitors such as anakinra (recombinant interleukin-1 receptor antagonist), canakinumab (monoclonal interleukin-1 antibody) and rilonacept (soluble interleukin-1 decoy receptor) reduce inflammation and are a safe and efficacious albeit off-label treatment option in the management of acute gout in patients with advanced CKD. The usual dose of anakinra for the management of acute gout is 100 mg daily, however, some experts recommend reducing the dose of anakinra in patients with GFR < 30 mL/min/1.73 m^2 to 100 mg every other day due to its renal clearance, unfortunately, there is no data presently to compare various doses of anakinra in these patients and it continues to be dosed based on physician and patient preference (Table 1).

It should be noted that anakinra is used intravenously in much higher doses for Macrophage Activation Syndrome and a dose reduction for gout in CKD may not be required [41]. Anakinra seems to be a safe and effective short-term therapy for acute gout in patients on dialysis and kidney transplant recipients based on small case series [42]. A dose reduction is not required for canakinumab or rilonacept for the management of acute gout in patients with advanced CKD. Despite the safety and efficacy of these drugs, lack of accessibility and high cost have limited their use, and they are currently recommended as second-line treatment in the management of acute gout, even in patients with advanced CKD [43]. The adverse effects of interleukin-1 inhibitors, although infrequent, include injection site reactions and infections [39]. Their safety profile makes them attractive options for hospitalized patients with uncontrolled DM or heart failure.

Adrenocorticotropic hormone

ACTH belongs to the melanocortin group of proteins that activate 5 melanocortin receptors (MC-R). ACTH is the only ligand for MC-2 R located on the adrenal glands and this binding stimulates adrenal corticosteroid release. However, ACTH is believed to possess steroid-independent anti-inflammatory properties. In the periphery, ACTH binds the MC-1 R and MC-2 R downregulating transcription factor NF-κβ, inhibiting the expression of proinflammatory cytokines and adhesion molecules [44]. ACTH, administered either subcutaneously or intramuscularly, has been used for managing acute gout off-label, especially in patients who are unable to tolerate oral medications or in patients where other agents are contraindicated due to comorbidities. A review of 181 acute gout patients, 34% with CKD stages 3–5 treated with synthetic ACTH at a dose of 1 mg demonstrated a 77% response rate. Additionally, over 80% of non-responders responded to a second dose administered the following day [45]. Synthetic ACTH is available in the European Union as Tetracosactide. Currently, no dose adjustments are recommended for advanced CKD patients. The duration of treatment with ACTH should be carefully monitored to prevent complications from long-term use such as suppression of the hypothalamic-pituitary-adrenal axis, DM, and ocular side effects such as cataracts and macular exudates [46].

Prophylaxis to prevent gout flares in patients with advanced CKD

The ACR guidelines for the management of gout (2020) recommend prophylaxis for all patients initiating ULT [23]. The thought behind initiating prophylaxis is to prevent gout flares due to fluctuations in sUA caused by initiating ULT. The agents used for prophylaxis stabilize the subclinical inflammation that may be present in inter-critical periods. Prophylaxis is usually continued for as long as there is evidence of ongoing disease activity such as gout flares or the presence of tophi and/or until 6 months after the target sUA has been achieved [19]. Although the use of musculoskeletal ultrasound for diagnosing gout is established, it may be used to monitor the response to ULT. Achieving low serum urate is associated with the resolution of tophi and the double contour sign on ultrasonography [47]. While musculoskeletal ultrasound allows for affordable and repeated use, additional studies are needed to determine the degree of tophus or double contour sign resolution required for the safe discontinuation of gout flare prophylaxis. Drugs typically used for prophylaxis include NSAIDs, colchicine, glucocorticoids, and interleukin-1 inhibitors. Chronic NSAIDs are contraindicated for gout flare prophylaxis in advanced CKD [34].

Colchicine

For patients with normal renal function, colchicine is dosed at 0.6 mg twice daily. For those with CKD, it is reduced to once daily, and for advanced CKD, to once every 2–3 days and the dose lowered to 0.3 mg (Table 2). The recommended dose for prophylaxis in patients on dialysis is 0.3 mg twice weekly (Table 2). As mentioned above, colchicine should be used with great caution in transplant patients taking strong inhibitors of P-glycoprotein or CYP3A4 such as cyclosporine and tacrolimus respectively [38]. The risk of colchicine toxicity is markedly increased in patients with advanced CKD or on dialysis or renal transplant recipients [48, 49].

Table 2. Overview of drugs used for gout flare prophylaxis

Drug	Dosing regimen for gout flare prophylaxis			
	Normal renal function	Advanced CKD (eGFR ≤ 30 mL/min/1.73 m^2)	Dialysis	Renal transplant
Colchicine	0.6 mg once or twice daily	0.3 mg daily or 0.6 mg every other day or thrice weekly	0.3 mg twice weekly	Avoid secondary to interactions with several drugs used in transplant recipients
Prednisone	5–10 mg daily	5–10 mg daily	5–10 mg daily	5–10 mg daily
Anakinra	100 mg SC daily	100 mg SC daily or 100 mg every other day	100 mg SC daily or 100 mg every other day	100 mg SC daily
Rilonacept	160 mg SC once weekly	160 mg SC once weekly	160 mg SC once weekly	160 mg SC once weekly

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SC: subcutaneous

Hypertension and hyperlipidemia are common in CKD and some CYP3A4 inhibitors [diltiazem, verapamil and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors] are used in the treatment of these comorbid diseases. The addition of colchicine to CYP3A4 inhibitors or vice versa may lead to toxicity manifested by vomiting, diarrhea, myopathy, neuropathy and rhabdomyolysis. Screening for colchicine toxicity with complete blood cell count and creatine kinase (CK) every 6 months was recommended for patients on prophylactic colchicine with CKD [49, 50]. However, it should be noted that an intercurrent illness, worsening of renal disease or addition of an offending medication may result in the acute onset of toxicity within days to weeks that monitoring every 6 months would not identify. Providers should remain vigilant in reviewing any medication changes, the development of an acute intercurrent illness or for early signs of toxicity (vomiting or diarrhea) in their patients with gout and CKD and should maintain a low threshold for discontinuing colchicine [48].

Glucocorticoids

Low-dose prednisone (5–10 mg/day) is considered safe for prophylaxis in advanced CKD (Table 2). However, monitoring for the development or worsening of DM or hypertension should be considered. Chronic low dose glucocorticoids increase the risk for osteoporosis and appropriate treatment, or monitoring may be necessary [51].

Interleukin-1 inhibitors

Interleukin-1 inhibitors, such as anakinra and rilonacept can be safely used off-label for prophylaxis of gout in patients with advanced CKD. Anakinra was successfully used to prevent recurrent acute gout attacks in a report of three patients [52]. Initially used to treat the acute gout attacks in patients with chronic gout, anakinra was continued at 100 mg daily while the dose of ULT was optimized, in one patient flares were prevented even with dose reduction to every third day [52]. However, the frequent dosing of anakinra makes it cumbersome for long-term treatment, thus, longer-acting agents such as rilonacept are sometimes preferred for prophylaxis (Table 2) [53, 54].

Urate-lowering therapy in patients with gout and advanced CKD

The goal for the long-term management of gout is to prevent gout flares, this can be achieved by lowering the sUA to less than 6.0 mg/dL or 5.0 mg/dL for tophaceous disease [55]. The xanthine oxidase inhibitors allopurinol and febuxostat are established therapies for this purpose. These drugs are underutilized in patients with advanced CKD due in part to safety concerns, more specifically cardiovascular events noted in febuxostat studies and the risk of allopurinol hypersensitivity syndrome (AHS) [56, 57]. Probenecid, a uricosuric agent, works by increasing tubular excretion of uric acid and requires functioning kidneys thus inappropriate in advanced CKD [23].

Allopurinol

Allopurinol is an analogue of hypoxanthine and is metabolized to oxypurinol which inhibits xanthine oxidase preventing the formation of uric acid [58]. Allopurinol is effective in reducing acute attacks and tophi if the recommended target sUA of < 6.0 mg/dL (< 0.5 mg/dL for tophaceous disease) is achieved [23, 24]. Although the United States Food and Drug Administration (FDA) approves allopurinol up to 800 mg daily, many clinical trials have used a maximum dose of 300 mg, consequently practitioners do not prescribe the higher doses required to achieve the target sUA leading to the undertreatment of gout [59]. Allopurinol is well tolerated and although skin reactions are reported in 13% of patients, severe reactions are extremely rare < 0.003 [60]. Oxypurinol, the active metabolite of allopurinol, is predominantly eliminated by the kidneys leading to safety concerns in patients with advanced CKD.

There are no randomized trials evaluating the effectiveness and safety of allopurinol in patients with gout and CKD ≥ 4, however, the STOP gout trial that compared allopurinol to febuxostat included patients with stage 3 CKD [60]. Both allopurinol and febuxostat decreased sUA and controlled flares in the stage 3 CKD patients as effectively as those with normal renal function. These results provide some reassurance for studying allopurinol in more advanced renal disease.

Although rare, AHS remains a major deterrent to its use in advanced CKD. Retrospective studies provide evidence that these reactions are more likely with higher starting doses of allopurinol > 100 mg/day and adjusting the dose to 1.5 mg per unit of eGFR maybe safe [57, 61]. Further caution should be exercised in patients with advanced age or those with the *HLA-B*5801* gene, which is most common in Asians (Koreans, Han Chinese and Thai) and African Americans. These factors represent additional risks for developing AHS [62]. Patients with moderate to severe renal disease (CKD ≥ stage 3) are at greater risk for the progression of gout and development of tophi, consequently the ACR recommends initiating allopurinol after the first gout attack for this group [23, 25, 26]. It is, nevertheless, imperative to adopt the treat-to-target approach to achieve the best results from allopurinol even in the presence of advanced CKD [23, 24]. Additional evidence for the safety of allopurinol in patients with CKD stage 3 and 4 is provided by the CKD-FIX trial that was designed to examine the renal protective effect of allopurinol in patients with hyperuricemia but without gout and although it was a negative study it is reassuring that a renal safety signal was not identified [63]. However, the STOP gout study reported more episodes of AKI in the allopurinol arm compared to febuxostat [60]. It is unclear if this is related to congestive heart failure and diuretic use (there were more patients with CHF randomized to allopurinol) or if there was a role for allopurinol. Despite these concerns allopurinol remains a ULT option for patients with gout and advanced CKD. However, the starting dose should be reduced to 50 or 100 mg daily or even every other day in patients with advanced CKD (Table 3). The dose should be titrated every 4 weeks to achieve the target of < 6.0 mg/dL monitoring complete blood counts, serum creatinine and hepatic transaminases for signs of toxicity.

Table 3. Overview of urate-lowering therapy for gout

Drug	Dosing regimen for urate-lowering therapy			
	Normal renal function	Advanced CKD (eGFR ≤ 30 mL/min/1.73 m^2)	Dialysis	Renal transplant
Allopurinol	Starting dose 100 mg daily. titrate to target (maximum dose 800 mg daily)	Starting dose 50–100 mg daily or every other day. Titrate to target	50–100 mg after dialysis. Titrate to target	Starting dose 50–100 mg daily. Titrate to target
Febuxostat	Starting dose 40–80 mg daily. Titrate to target (maximum dose 120 mg daily)*	Starting dose 20–80 mg daily. Titrate to target	Starting dose 20–80 mg daily. Titrate to target	Starting dose 40–80 mg daily. Titrate to target
Pegloticase	8 mg IV every 2 weeks	8 mg IV every 2 weeks	8 mg IV every 2 weeks	8 mg IV every 2 weeks

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IV: intravenous. * Food and Drug Administration approved the maximum dose of febuxostat at 80 mg daily

Febuxostat

Febuxostat is a potent non-purine analogue inhibitor of xanthine oxidase [64]. In contrast to allopurinol, it is metabolized by glucuronidation and oxidation in the liver and its serum urate-lowering ability is not modified in renal disease [65]. Febuxostat at doses of 80 mg and 120 mg daily proved efficacious in lowering sUA, reducing flares and tophus size, however, 80 mg daily is the maximum dose approved in the US due to concerns of cardiovascular disease [56, 59]. The efficacy of febuxostat in stage 4 CKD was demonstrated in one randomized trial and evidence of efficacy for advanced renal disease was reported in a few retrospective studies [66–68]. The starting dose for febuxostat ranged from 40 to 80 mg/day however in the retrospective study by Juge et al. [66] a few patients were started at 120 mg/day. Like allopurinol, febuxostat may be used in patients with advanced CKD. However, a lower starting dose of 20 to 40 mg daily may be prudent, and the dose similarly titrated to achieve the target sUA (Table 3).

Both allopurinol and febuxostat have been shown to be safe and effective in kidney transplant recipients [69]. Oxypurinol is readily dialyzable leading to the suggestion that allopurinol should be dosed post-dialysis (Table 3) [70]. Concomitant use of allopurinol or febuxostat with azathioprine is not recommended in renal transplant recipients due to the risk of bone marrow suppression [71]. This is not an issue with mycophenolate.

Gout is associated with hypertension DM and cardiovascular disease in addition to renal disease. The results of the CARES trial raised concerns of increased cardiovascular mortality with febuxostat resulting in a black boxed warning from the FDA [56]. However, 56% of subjects in CARES did not complete the study and the results of two subsequent studies, the FAST and STOP Gout trails did not reveal a cardiovascular safety signal for febuxostat relative to allopurinol in patients with gout [60, 72].

Febuxostat and allopurinol are often discontinued or held due to concerns of worsening CKD although it is actually hyperuricemia that is associated with the progression of renal disease [73, 74]. Several recent large trials examined the ability of both allopurinol and febuxostat to slow the progression of CKD. The FEATHER trial enrolled 467 patients with asymptomatic hyperuricemia and stage 3 CKD to receive febuxostat or placebo for 108 weeks. Although there was no benefit, the stability of kidney function over the study is reassuring for patients with gout and CKD [75].

Pegloticase

Pegloticase is a recombinant mammalian uricase linked to polyethylene glycol. It rapidly degrades uric acid to allantoin that is more soluble and easily excreted by the kidneys. Pegylation prolongs the half-life to 14 days, allowing it to break down uric acid decreasing the plasma levels to undetectable encouraging the translocation of tissue uric acid to the plasma compartment [76]. The result is a significant decrease in total body uric acid and resorption of tophi. A post hoc subgroup analysis of patients with stage 3 or 4 CKD enrolled in 2 pivotal trials was performed. Pegloticase was equally efficacious in lowering sUA regardless of stage of CKD and renal function was unchanged throughout the six-month trial and the 2.5-year open-label extension [77]. Unfortunately, only 42% of patients treated with pegloticase maintain uric acid < 6.0 mg/dL and 26% suffered infusion reactions [78]. Both events are attributable to the development of antidrug antibodies. The addition of methotrexate 15 mg weekly starting 4 weeks prior to the pegloticase improved efficacy to 78% and reduced infusion reactions to 7.1% [79]. Methotrexate is contraindicated in advanced CKD and would not be an option to improve the efficacy of pegloticase in this group. Mycophenolate mofetil (MMF) an immunosuppressant administered 2 weeks prior to pegloticase was more effective compared to placebo at 12 weeks in maintaining uric acid < 6.0 mg/dL and reducing infusion reactions [80]. In an open-label study with 10 patients co-treated with leflunomide and pegloticase 70% were able to continue on therapy with therapeutic sUA for 26.6 ± 14 infusions [81, 82]. In a small open-label phase 4 trial. Pegloticase seemed to be safe and effective in reducing urate levels in kidney transplant recipients with uncontrolled or tophaceous gout [83]. The standard pegloticase dosing of 8 mg every 2 weeks may be used in patients with advanced CKD, on dialysis or renal transplant recipients (Table 3).

Management of cardiovascular risk in patients with hyperuricemia and CKD

Gout is associated with DM, hypertension, metabolic syndrome and cardiovascular disease. The role these metabolic diseases play in the development of hyperuricemia and gout was recently reviewed [84]. Hyperuricemia and gout are associated with an increased risk of cardiovascular events, especially in patients with CKD. This is primarily thought to be due to hyperuricemia-induced activation of the renin-angiotensin-aldosterone system, oxidative stress, and reduction of nitric oxide in the endothelium, thereby leading to renal vascular changes causing impairment of renal blood flow and development of kidney disease and resultant hypertension [29, 85]. Other mechanisms include the stimulation of cyclooxygenase 2 and thromboxane further enhancing vasoconstriction and platelet activation and the production of monocyte chemoattractant protein-1 that may induce vascular smooth muscle cell proliferation [86]. This highlights the importance of cardiovascular risk reduction in patients with hyperuricemia and gout to prevent morbidity and mortality from cardiovascular disease.

The effect of ULT on cardiovascular risk reduction, especially in patients with CKD, is unclear at present. The All-HEART study included over 5,000 patients followed for a mean of 4.8 years failed to show any benefit of allopurinol 600 mg daily vs. placebo in reducing non-fatal myocardial infarction, stoke or cardiovascular death [87]. Pharmacological agents that have shown benefits in reducing cardiovascular risk in patients with gout include losartan, an angiotensin receptor blocker, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Many studies have shown the beneficial effect of losartan in preventing morbidity and mortality associated with cardiovascular disease. Though losartan is well known to have a modest urate-lowering effect and is currently recommended as the antihypertensive of choice in patients with gout, it has to be used with caution in patients with advanced CKD [23]. Multiple analyses have demonstrated that SGLT-2 inhibitors such as empagliflozin and ertugliflozin, through their uricosuric effect, lower serum urate levels and the incidence of gout episodes and have been significantly associated with reduction in adverse cardiovascular events and improvement in renal outcomes [88, 89].

Similar to MSU crystals, cholesterol crystals can promote NLRP3 inflammasome activation of IL1-β promoting atherosclerosis [90]. The CANTOS trial demonstrated that by suppressing inflammation with canakinumab, a monoclonal antibody targeting IL1-β recurrent cardiovascular events could be reduced [91]. However, canakinumab was associated with more deaths related to infections or sepsis. Colchicine, another anti-inflammatory therapy used in the treatment of acute gout has pleiotropic cellular effects including inhibition of tubulin polymerization [92]. Colchicine 0.5 mg daily was associated with a reduction in cardiovascular events compared with placebo in patients with prior cardiovascular disease [93]. Patients with moderate to severe kidney disease were excluded from this trial so it remains unknown if colchicine dose adjusted for advanced CKD would retain the same beneficial cardiovascular properties.

Future directions in the management of gout in patients with CKD

Patients with gout frequently have comorbidities like CKD that limit treatment options due to increased incidence of serious adverse events. Additionally, these patients are generally on other medications that may interact with the drugs prescribed for gout. Therefore, research is needed to develop novel therapeutics for use in these scenarios. So far, certain drugs have shown promising effects in gout-directed therapy in patients with normal and mildly reduced renal function.

Benzbromarone, a urate-lowering agent that exerts its clinical activity through its uricosuric effect, has shown efficacy in stage 3 CKD and might be nephroprotective. It was never approved by the FDA and was withdrawn by the manufacturer in 2003 due to concerns of hepatotoxicity, however, recent studies have shown efficacy in lowering sUA and serum creatinine [94]. AR882 is a selective uric acid transport 1 (URAT1) inhibitor that retains efficacy in moderate CKD [95]. Topiroxostat is a xanthine oxidase inhibitor whose pharmacokinetics are not affected by mild to moderate renal impairment. Dotinurad is a novel selective urate reabsorption inhibitor that has shown urate-lowering activity even in mild to moderate renal impairment. ALLN-346 is an engineered urate oxidase that works in the gut and can bypass the innate

renal excretion mechanisms and could potentially be used in patients with advanced CKD and end-stage renal disease. This agent is in phase 2 of development for the treatment of hyperuricemia in patients with gout and advanced CKD [96].

Although the newer agents that we discussed can potentially be used in patients with mild CKD, further studies are warranted to learn about the pharmacokinetics and adverse effect profiles of these medications so that they can then be safely administered in patients with advanced CKD.

Conclusion

Gout is the most common inflammatory arthritis and is associated with several comorbidities including cardiovascular and renal disease. Advanced CKD is associated with more severe gout, however, with appropriate adjustment and monitoring many of the therapeutic interventions may be used in this population. We have reviewed the management of gout and suggested how best to use currently available treatments in patients with advanced renal disease.

Abbreviations

ACE: angiotensin-converting enzyme

ACR: American College of Rheumatology

ACTH: adrenocorticotropic hormone

AHS: allopurinol hypersensitivity syndrome

AKI: acute kidney injury

CKD: chronic kidney disease

DM: diabetes mellitus

eGFR: estimated glomerular filtration rate

EULAR: European Alliance of Associations for Rheumatology

FDA: Food and Drug Administration

MSU: monosodium urate

NF-κβ: nuclear factor kappa-B

NLRP3: Nod-like receptor family pyrin domain-containing 3

NSAIDs: nonsteroidal anti-inflammatory drugs

SGLT-2: sodium-glucose co-transporter-2

sUA: serum uric acid

ULT: urate-lowering therapy

Declarations

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily represent those of the Department of Veterans Affairs or the United States Government.

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